Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Comments to: Docket No. 2004D-0187,
Draft Guidance for Industry on Premarketing Risk Assessment,
69 Federal Register: Pgs 25130-25132

From: Eli Lilly and Company

Eli Lilly and Company (Lilly) appreciates the opportunity to offer the following comments to FDA Docket No. 2004D-0187, Draft Guidance on Premarketing Risk Assessment. Lilly agrees with and supports the comments submitted by the Pharmaceutical Research and Manufacturers of America. The few comments of ours that duplicate ones included in their comments are intended to reinforce their importance. Our comments consist of general comments on the guidance papers, followed by general and specific comments on the individual guidance paper.

Lilly compliments the FDA on:

1. Separating risk assessment and risk management
2. Recognizing that risk assessment is iterative throughout a product's life cycle
3. Focusing risk minimization efforts on known safety risks
4. Eliminating references to different "levels" of risk management interventions
5. Recognizing that for most products FDA-approved professional labeling will be sufficient for risk minimization. We suggest that Patient Package Information be explicitly included as a tool whose use would not be considered to constitute a RiskMAP.

Lilly would like to express the following general concerns and suggestions:

1. Please provide clearer guidance and criteria (a unifying concept) to help companies determine when a RiskMAP should be prepared and submitted. For example, a unifying concept could be expressed as "Consider using more than routine labeling and pharmacovigilance when the number or severity of a product's risks appears to undermine the magnitude of its benefits in an important segment of potential or actual users".
3. The guidances should explicitly state that the information concerning RiskMAP tools that is made publicly available will not divulge any company's proprietary information.
4. Although the target number or rate of occurrence of the risk that is attempting to be minimized, can, as an ideal, be set at the theoretical "zero", such an approach is neither

practical nor informative with regard to setting a threshold for subsequent action. The guidances should explicitly acknowledge this point and direct sponsors and regulators to engage in open dialogue to establish a realistic target value for the risks being minimized.

5. FDA authority to impose requirements in this area needs to be understood, particularly when imposing requirements (other than labeling) on products that otherwise meet the statutory standard of "safe" (for instance, a manufacturer is required to *verify* that patients obtain lab tests prior to using product).
6. The guidances should be explicit in stating that sponsors of generic products will be held to the same risk-management standards as sponsors of the innovator product. This should be applied to both risk management elements that are contained in the label (and thus generic should be required to copy) as well as risk management elements (including RiskMAPs) that go beyond labeling.

General comments for Docket No. 2004D-0187, Draft Guidance for Industry on Premarketing Risk Assessment

1. We compliment the FDA on their focus on minimizing potential for medication errors using medication error prevention analysis (MEPA) and Failure Mode and Effects Analysis (FMEA), and their recognition of current efforts in this regard.
2. We agree with the proactive approach to anticipating safety questions and planning safety data collection and analysis across the entire development plan. However, the guidance on pre-marketing risk assessment focuses on phase 3 studies. Risk anticipation and assessment are also important in phases 1 and 2. We suggest that the guidance document also advise sponsors to anticipate potential issues and risks and incorporate appropriate data collection into their early phase trials, and institute appropriate risk management interventions into clinical trials when appropriate. In addition, pharmacoepidemiologic studies could provide: information on understanding disease and safety endpoints, support for clinical trail protocol design and interpretation of comparator studies, a baseline reference for comparison to post-marketing experience, prediction (identification) of risk factors, and prediction (identification) of specific sub-populations at risk
3. We agree with the concept of exploring temporal relationships between product exposure and adverse events
4. We suggest including an exploration of exposure-response relationships as part of the assessment of the causality of adverse events. A population PK approach would be quite helpful in this regard, as well as larger clinical pharmacology studies that deal with maximal exposure, eg. QTc studies.
5. The guidance document refers to the possibility of retrospectively linking pharmacogenomics markers to serious adverse events. However, no reference is made to situations where pharmacogenomics identifies groups of subjects with high exposures. Both positive and negative correlations could be made, and it would be helpful to know what kind of criteria FDA would apply to safety data from such a study and how they would weigh the significance of a positive or negative correlation.

6. In discussions of causality, we recommend consideration of the correlation of the dechallenge time course and PK elimination profile of parent compound and metabolites as being somewhat helpful for events not considered to be related to withdrawal.
7. It would be helpful to have FDA-industry consensus on practical and safe guidance on where and when challenge and dechallenge protocols might be useful in making or refuting causality attributions.
7. We are concerned that having the availability of a safe and effective alternative to the investigational product be a specified circumstance that would call for a larger safety database amounts to establishing a new standard of approval reserved for product that are not first-in-class. We do not believe that such a new standard is appropriate.
8. We do not believe that it is ethical, in most circumstances, to use a placebo control in long-term, controlled safety studies. The guidance should clarify that placebo control should be used in these studies only when ethically appropriate.
9. We are concerned that delaying final dose selection until phase 3 will increase the complexity of these trials, and increase the level of uncertainty on the part of study subjects that they are getting "active" treatment. Each of these factors will contribute to a delay in final delivery of effective therapy to patients. The guidance should recognize that in most instances effective dose selection can be performed in phase 2.
10. We request that FDA help establish, and make publicly available, groupings of MedDRA terms that would serve as case definitions for commonly reviewed signals and adverse events. This may be accomplished via an agency-industry collaboration.

Line specific comments for Docket No. 2004D-0187, Draft Guidance for Industry on Premarketing Risk Assessment

1. Line 434 For international studies there are conflicting national rules governing obtaining and using reserved blood samples that reflect their national policies on privacy and informed consent. The guidance should recognize these conflicting rules and acknowledge that their observance may interfere with the sample collection recommended in this section, perhaps even stating that such samples may be collected only in those legal jurisdictions in which they are permitted and that this would not compromise the overall study.
2. Line 581 Does the recommendation to use one coding convention throughout a clinical program permit updating the MedDRA dictionary as new versions become available? Lilly recommends that updates to the MedDRA dictionary be permitted during a development program, that sponsors need to specify which version was used for analysis of individual studies and the integrated safety database, and that sponsors do not need to reconcile differences between individual study analyses and the integrated analyses that are driven by use of different MedDRA versions.
3. Line 603 We recommend that the guidance make clear that consultation with the FDA to re-characterize an event to make it consistent with accepted case definitions can be conducted either "real-time" or as a group review at the time of integrated analysis of a clinical trial or development program, depending on the both the urgency of the need for clarification and when the need for clarification is noted?

4. Line 756 We recommend that the guidance acknowledge that while "cut point" analyses appear to be useful there may not be enough patients in the border zones to permit valid statistical analyses. Sample size for the study should not be driven by the need to populate these "cut-point" zones.
5. Line 879 Please provide guidance on how to use the criteria that will be considered to define the duration of post-therapy follow-up that will be needed to detect late safety events. Even a comment that selection of the duration of post-treatment follow-up should be done in consultation with the FDA would be helpful in placing this item on an agenda for a sponsor-FDA meeting.

Regards,

Paul R. Eisenberg, M.D.
Vice-President
Global Product Safety
Eli Lilly and Company